Pharmacologic Agents for the Management of Asthma in Aircrew

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INTRODUCTION

Asthma is an inflammatory condition of the airways, producing variable bronchoconstriction. First line therapy is directed at controlling the inflammatory process with agents such as inhaled steroids, nedocromil, and the newer leukotriene inhibitor drugs. In severe cases, systemic steroids or other immunosuppressive therapies may be required for suppression of inflammation.

Other agents provide symptomatic relief of bronchospasm. Short-acting beta-agonists are the mainstay for providing relief of acute episodes. Anticholinergic inhaled agents have a minor role in acute episodes. Long-acting beta-agonists are used to smoothe long-term symptom control and help reduce the frequency of acute episodes when combined with inhaled steroids. Theophylline has bronchodilator properties and may have anti-inflammatory properties, but has a narrow therapeutic window.

Other newer agents are currently being developed, including anti-immunoglobulin E, antitryptase and anti-CD4 agents. These newer agents may expand the options for control of asthma over the next decade.[13]

The prevalence of asthma has been increasing in recent years, and occurs not uncommonly in an aviator population. Evaluation of aircrew requires a comprehensive respiratory assessment, including a detailed history of symptoms, triggering factors, and past treatment requirements, and a pulmonary function assessment with evaluation of bronchial reactivity. The challenge for the flight surgeon is to define as clearly as possible the severity of the disease, and to control the condition with agents acceptable for continuing aircrew duties. Good control of the inflammatory process with inhaled steroids alone, while minimizing or eliminating the need for bronchodilators, may allow continuing aircrew duties. The purpose of this monograph is to provide an overview of the agents currently available for the control of asthma from an aeromedical perspective. Reference (17) is a website providing excellent background information for both patients and physicians on asthma. Reference (10) provides a more comprehensive overview of the assessment and treatment of asthma in aircrew. In fast-jet aircrew, any degree of asthma is generally unacceptable because varying degrees of small-airway dysfunction may predispose to airway collapse with +Gz, thus contributing to both acceleration atelectasis and aggravation of the ventilation/perfusion mismatch induced by G. In non fast-jet aircrew, stability of bronchial reactivity and full control of asthmatic symptoms with acceptable medications is the prime objective. Aircrew whose airway reactivity is normalized and well-controlled on acceptable medications may be considered for continuing duties.

PHARMACOLOGIC AGENTS

Inhalation Delivery Devices

Most asthma medications are delivered through inhalation delivery devices. For decades, the standard delivery device has been the pressurized metered dose inhaler (MDI). For many patients, drug delivery with MDIs is improved significantly by the use of a spacer device. Chlorofluorocarbons (CFCs) have been the primary propellants for MDIs since their introduction over three decades ago. However, due to environmental concerns, CFCs are being phased out as MDI propellants, and are being replaced generally by hydrofluoroalkanes (HFAs). Environmental concerns aside, HFAs have several therapeutic advantages over CFCs. MDIs with HFAs demonstrate an improved consistency in delivered dose per actuation, and administer a warmer spray with reduced jetting velocity. HFAs also have a smaller particle size, resulting in better delivery of medication farther into the lungs.[14] Inhaled agents may also be delivered by dry powder

inhalers (DPIs). These devices deliver medication from either capsules, a bulk reservoir, or as multi-dose units. DPIs may be battery-powered or patient-driven. The latter are dependent on the patient's inspiratory effort for proper deposition. These are activated by inspiration itself, and may be easier to use for patients with difficulty with hand-breath co-ordination.[8]

The type of device, the drug formulation, and patient technique are all variables that determine the dose of inhaled drug that reaches the lungs – variables that must be kept in mind when assessing patient response and potential medication side-effects. In particular, both flunisolide and beclomethasone are soluble in HFAs, but insoluble in CFCs; thus, HFA MDIs result in much greater delivery of these drugs to the lungs. This greater deposition results in an approximately 2.6 fold increased dose. Several studies with the newer MDIs support equal efficacy using half the apparent dose of the older CFC powered inhalers.[14] With the gradual phase-out of CFCs in favor of HFAs, flight surgeons must be aware of and assess the change in relative potency of the various preparations of inhaled steroids in particular.

BETA-AGONISTS

$Beta_2$ agonists are sympathomimetic amines which, despite variable degrees of beta-selectivity, display similar effects, such as cardiac excitation, CNS stimulation, and vasoconstriction, and similar side-effects, such as tremor, nervousness, headache, sweating, and increased heart rate and blood pressure. The requirement for beta-agonists indicates that the underlying inflammatory process is not fully controlled, and beta-agonists are required to provide either acute symptom control, in the case of short-acting agonists, or longer-term control of bronchoconstriction with long-acting agents.

Short-acting Agents

Short-acting beta-adrenergic stimulants provide rapid relief from acute bronchospasm. Non-selective agents such as isoproterenol have been superseded by relatively selective $beta_2$ agonists including terbutaline, isoetharine, and albuterol (salbutamol). Administered by MDI, these agents have a rapid onset (~15 minutes), and a relatively short duration of action (3-4 hours). Even with inhalation, there is some systemic absorption of these drugs, with side-effects including tachycardia, palpitations, headache, sweating, nervousness, and tremors. Oral preparations are also available, but have a slower onset of action (~1 hour), longer action (5-7 hours), and more side-effects, and thus are not suitable for use in aircrew. Short acting agents may be all that is required for very mild asthmatics with very infrequent or very specific trigger factors (step 1 therapy).

Aeromedical Recommendations: **Because of the side effect profile, the use of short-acting inhaled beta-agonists in aircrew is not advised within six hours of duty. The requirement for these agents for symptomatic control of bronchospasm is generally an indication that the asthma is inadequately controlled for aircrew duties. An exception might be pure exercise-induced asthma, where inhaled ß-agonists may provide excellent control of exercise-induced bronchoconstriction, and may be suitable for "as required" use up to six hours pre-flight, except in fast-jet aircrew, where the heavy exertion of anti-G straining maneuvers could precipitate bronchospasm and the sympathomimetic effect may aggravate G-related arrhythmias.**

Long-acting Agents

In the past decade, long-acting inhaled $beta_2$ agonists such as salbuterol and formoterol have been introduced to provide a more sustained action for control of bronchoconstriction. They are not intended for acute symptomatic relief of bronchospasm. A common current clinical approach is to combine a long-acting inhaled agent with an inhaled steroid if adequate control is not achieved with the steroid alone. A recent study, dispelling earlier concerns that regular beta-agonist treatment might cause a worsening of asthma, demonstrated better control of asthma when inhaled corticosteroids were combined with formoterol than with short-acting albuterol.[9]

Although cardiovascular and other non-pulmonary side-effects, largely related to direct cardiac stimulation, reflex activation of adrenergic mechanisms, and hypokalemia, are a concern with all beta-adrenergic agonists, the inhaled $beta_2$-agonists have proven in several clinical trials to be remarkably free from cardiovascular side effects in patients followed with ECGs and Holter monitoring.[6,15] In a group of patients with mild asthma, low (12 μg) doses of formoterol showed no cardiovascular side effects compared with placebo, although at higher doses (up to 96 μg), heart rate and blood pressure were increased, QT interval increased, blood glucose increased, and serum potassium decreased compared with placebo.[3] In

COPD patients with co-existing hypoxia, formoterol in a 24 µg dose was shown to significantly reduce serum potassium level, and increase ventricular and supraventricular ectopic activity.[5]

Aeromedical recommendations: **These long-acting highly selective beta-agonists have added a significant bullet to the pharmacologic armamentarium for maintenance control of asthma. Further assessment is required before these agents can be recommended for use in aircrew, especially in pilots. Based on the presently available clinical information, they might be considered for non-pilot aircrew in non-fast jet operations, in lower doses only, e.g., 50 µg of salmeterol or 12 µg of formoterol. The sustained beta-adrenergic stimulation induced by these agents may predispose to arrhythmias and other undesirable side effects in high-G operations, and their use in fast-jet aircrew cannot be recommended pending aeromedical evaluation.**

ANTI-INFLAMMATORY AGENTS

Steroids

Inhaled Steroids

Inhaled steroids form the mainstay for the treatment of asthma of all but very mild degree, where occasional use of inhaled short-acting beta-agonists may suffice. Inhaled steroids vary in potency but all act by suppressing airway inflammation, which is recognized as the primary mechanism in asthma. Apart from local upper airway irritation and infrequent oral candidiasis, inhaled steroids are generally free from side effects. Treatment is initiated at a low dosage, e.g., 400-800 µg daily of beclomethasone or equivalent, and the dosage titered upwards if symptoms and airway reactivity are not adequately controlled. In high dosages, inhaled steroids may suppress the adrenocortical axis, a potentially significant aeromedical concern, exposing aircrew to the risk of adrenal crisis at times of high stress. Decreased bone density, cataract formation, dermal thinning and glaucoma have also been reported.[8]

Doses of beclomethasone or budenoside of 1500 µg per day or higher have been shown to suppress hypothalamo-pituitary-adrenal axis (HPA) function,[1] although there is wide inter-individual variation,[2] with some individuals maintaining normal HPA function with dosages as high as 5 mg (5000µg) daily. However, in aircrew, dosages exceeding 1200 µg of beclomethasone or equivalent are not recommended; if additional maintenance medication is required, a long-acting beta-agonist (see above), or leukotriene inhibitor (see below) may be considered. (Note: The studies quoted were based on the use of CFC MDIs, and as noted earlier the possibility exists of altered absorption of inhaled steroids with HFA MDIs).

Aeromedical recommendations: **In moderate dosages, i.e., up to 1200 µg per day of CFC MDI beclomethasone or equivalent, inhaled steroids appear to be safe for use in all aircrew, including pilots. These drugs should form the first line Step 2 treatment for asthma in aircrew requiring more than very infrequent short-acting beta-agonists for control (Step 1 Rx). Good control of airway inflammation with inhaled steroids may well result in stabilization and normalization of airway function, including airway reactivity, and may allow aircrew including pilots to return to flying duties in other than fast-jet operations. This should be confirmed by a full pulmonary function assessment as part of the aeromedical disposition work-up; such testing should be carried out with the aircrew member taking his usual maintenance dose of inhaled steroid.**

Systemic Steroids

Although high-dose rapidly tapering oral steroids may be useful in the short-term suppression of an acute asthmatic episode, the requirement for systemic steroid therapy for maintenance control of asthma reflects a degree of asthma incompatible with all aircrew duties. Systemic steroids have side effects generally incompatible with aircrew duties, including psychotropic effects, hypertension, GI side effects including ulcers, bone mineral loss, and significant HPA suppression.

Aeromedical recommendations: **Aircrew should not be returned to flying duties while taking systemic steroids. The requirement for systemic steroids for control of an acute asthmatic episode should prompt a thorough aeromedical review with re-assessment of pulmonary function, including airway reactivity, before considering a return to flying duties.**

Nedocromil

Nedocromil is a non-steroidal pyranoquinolone anti-inflammatory agent which acts by stabilizing inflammatory cells, thus preventing the local release of inflammatory mediators and inhibiting

chemotaxis. It is administered by MDI at a dose of 4mg four times a day, or before exposure to precipitants such as exercise. Nedocromil is not as effective as inhaled steroids in reducing airway inflammation, but aside from bad taste, occasional headache, and GI upset, it is generally free from systemic side effects.

Aeromedical recommendation: Nedocromil may be helpful in some aircrew with mild asthma who require an anti-inflammatory inhaled medication to control airway reactivity, but better control is generally achieved with inhaled systemic steroids, and at less frequent dosing.

Disodium Cromoglycate

Disodium cromoglycate (DSCG) is an inhibitor of mast cell degranulation that can help decrease airway responsiveness. It has no bronchodilating activity and is useful only for prophylaxis. DSCG should not be added to an established regimen of inhaled glucocorticoids – it can neither augment nor sustain the improvement in airway responsiveness already achieved by inhaled glucocorticoids.[4] It has no systemic toxicity, and so is potentially a good drug for aircrew with mild asthma. Bad taste is virtually the only side-effect. Although it is not as effective as a beta-agonist, it may be helpful for preventing exercise-induced bronchospasm. For maintenance prophylaxis, the minimum effective dose is considered to be 10 mg 3-4 times daily. MDI formulations of DSCG contain only 1 mg per actuation, so effective adult dosages can really only be accomplished with a DPI capsule formulation, or a nebulizer.

Aeromedical recommendation: **DSCG is worth a trial for prophylaxis in aircrew with mild asthma symptoms because of its freedom from systemic side-effects.**

Theophylline

Theophylline has been a useful treatment for asthma for over 50 years, and although traditionally classified as a bronchodilator, has recently been shown to have immunomodulatory, anti-inflammatory and other non-bronchodilator properties that contribute to its efficacy as an anti-asthmatic medication.[16]

Aeromedical recommendation: Because of its markedly narrow therapeutic window, and significant side effects including cardiac arrhythmias, tremor, neuromuscular irritability and seizures, theophylline is not recommended for use in aircrew.

Leukotriene Inhibitors

Leukotrienes, along with prostaglandins and thromboxanes, belong to a group of biologically active fatty acids called eicosanoids. They are not stored in cells but are generated by lipoxidation of arachidonic acid. Leukotriene B_4, produced by neutrophils and monocytes, is chemotactic for neutrophils and causes leukocyte activation. Activated eosinophils and monocytes preferentially make cysteinyl leukotrienes, which are extremely potent bronchoconstrictive compounds. In addition, leukotrienes also increase vascular permeability, stimulate mucus release, and slow ciliary activity and mucus transport. Leukotrienes are thus central in the pathogenetic mechanism for the asthmatic response, and major efforts have been made to inhibit the synthesis of, or block the effects of, leukotrienes. This has led to the development of anti-leukotrienes, an entirely new and potentially extremely useful group of drugs in the anti-asthma armamentarium, which target specific sites in the inflammation cascade. Three of the currently available drugs are specific leukotriene D4 receptor (LTD4) antagonists, and the other is a 5-lipoxyenase inhibitor (see table below). Anti-leukotrienes are the subject of several recent major reviews.[7,11,12]

The anti-leukotrienes currently clinically available are in Table 1 (adapted from 12).

In antigen challenge studies, LTD4 antagonists inhibit 81% of the early airway response, and up to 57% of the late airway response. They can decrease airway responsiveness to methacholine, antigens, cold air, exercise, and aspirin in sensitive patients. A particular advantage is that they may also be effective for allergic rhinitis as well as asthma. Few studies have compared the effectiveness of these agents with other anti-asthmatic medications. The clinical effectiveness of LTD4 antagonists in asthma appears to be similar to low-dose inhaled steroids, nedocromil or cromoglycate

The established effects of the anti-leukotrienes are shown in Table 2 (adapted from reference 12).

Advantages/Disadvantages/Side-effects

- LTD4 antagonists have a rapid onset of therapeutic action (within 2 weeks), compared

with inhaled steroids, which may take up to six weeks to achieve full therapeutic benefit.

- Once or twice daily dosage may improve compliance.
- Oral delivery may produce more consistent therapeutic responses.
- They may be effective for allergic rhinitis as well as asthma.
- Side-effects have been minimal in initial clinical trials (2 years experience now).
  - Occasional headaches, nausea, diarrhea (incidence not different from placebo), with occasional mild elevation of liver enzymes, have been described.
  - Zafirlukast and pranlukast, but not montelukast, inhibit cytochrome p450 and may produce drug interaction effects.
  - A few cases of a Churg-Strauss-like syndrome have been reported in patients during initiation of zafirlukast, during tapering of systemic steroid dosages.

This new class of anti-asthmatic medications may be helpful in control, but not acute treatment, of asthma in mild or moderate cases, either as initial step 2 treatment or combined with inhaled steroids. They may also be used to achieve control with a lower steroid dosage in moderate to severe asthmatics. Improvement can be expected in approximately 50% of patients.

Aeromedical recommendation: Early clinical experience suggests these drugs are safe and moderately efficacious. There have been no trials published on possible effects on psychomotor or cognitive performance or vigilance, nor on other factors of aeromedical concern such as vision, special senses, or environmental effects. Until further clinical experience becomes available, the use of these agents cannot be recommended in pilot aircrew. In other aircrew, particularly in non-flight safety sensitive positions, consideration might be given to a trial of an LTD4 agent in step 2 control (requiring daily preventive medication).

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TABLE 1

Drug	Action	Status	Dosage	Cost (USD/month)
Montelukast (Singulair)	Leukotriene D4 receptor antagonist	Licensed worldwide	10 mg/day	75.80
Zafirlukast (Accolate)	Leukotriene D4 receptor antagonist	Licensed worldwide	20 mg BID	52.50
Pranlukast (Ultair)	Leukotriene D4 receptor antagonist	Launched in Japan	300-450 mg QD or BID	ND
Zileuton (Zyflo)	5-lipoxygenase inhibitor – inhibits leukotriene synthesis	Launched in US	600 mg QID	75.00

TABLE 2

	Montelukast	Pranlukast	Zafirlukast	Zileuton
Early response	Effective	Effective	Effective	Effective
Late response	Effective	Effective	Effective	Not effective
Bronchial hyper-responsiveness	ND	Effective (methacholine)	Effective (allergens)	Effective (cold air)
Exercise-induced asthma	Effective	Effective	Effective	Effective
Allergic rhinitis	ND	ND	Effective	Effective
ASA sensitivity	Effective	Effective	ND	Effective
Chronic asthma	Effective	Effective	Effective	Effective
Eosinophil level	Effective	Effective	Effective	Effective
Comparisons				
Inhaled steroids	Similar	Similar	Similar	ND
Nedocromil or cromoglycate	ND	Similar	Similar	ND
Theophylline	ND	ND	ND	Similar

ND = Not Demonstrated